



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of

COFFIN et al.

Atty. Ref.: 117-340

Serial No. 09/762,098

TC/A.U.: 1648

Filed: June 20, 2001

Examiner: Li

For: CELL LINES FOR THE PROPAGATION OF MUTATED HERPES
VIRUSES

June 29, 2004

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellants hereby appeal the final rejection of claims 34-46, in the Office Actions dated July 29, 2003 and March 23, 2004, and submits the present Appeal Brief, in triplicate, pursuant to Rule 192.

(1) REAL PARTY IN INTEREST

The real party in interest is BioVex Limited, 70 Milton Park, Abingdon, Oxford, United Kingdom OX14 4RX, by way of an Assignment from the applicants, recorded in

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the U.S. Patent and Trademark Office on June 20, 2001, at Reel 011937, Frame 0553, and a Change of Address submitted for recordation on April 7, 2004..

(2) RELATED APPEALS AND INTERFERENCES

The appellants, the undersigned, and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(3) STATUS OF THE CLAIMS

Claims 1, 3-5, 7-10, 27-33 and 47-58 are pending. Claims 1, 3-5, 7-10, 27-33 and 47-58 are canceled, without prejudice, in the attached Second Amendment Under Rule 116.

Claims 1, 3-5, 7-10, 27-33 and 47-58 have been finally rejected. Upon entry of the attached Second Amendment Under Rule 116, claims 34-46 will be pending and the subject of the present appeal.

Originally-filed claims 1-27 were amended in the Preliminary Amendment dated February 2, 2001 which also canceled claim 13, without prejudice.

Claims 2, 6 and 11-26 were canceled, without prejudice, claims 1, 3, 8, 9, 10 and 27 amended, and claims 28-58 added in the Amendment dated May 6, 2003.

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An Amendment Under Rule 116 dated December 1, 2003 and re-submitted by facsimile on December 29, 2003, which made amendments of the specification, has been entered. See, Advisory Action dated March 23, 2004.

Claims 1, 3-5, 7-10, 27-33 and 47-58 are canceled, without prejudice, in the attached Second Amendment Under Rule 116. Entry of the attached Second Amendment Under Rule 116 is requested. The attached Second Amendment Under Rule 116, by only canceling claims, will reduce the issues for appeal without raising new issues requiring further search and/or consideration.

Upon entry of the attached Second Amendment Under Rule 116, claims 34-46 will be the subject of the present appeal.

A copy of all the pending claims 34-46 is attached as Appendix A.

(4) STATUS OF THE AMENDMENTS

An Amendment Under Rule 116 dated December 1, 2003 and re-submitted by facsimile on December 29, 2003, which made amendments of the specification, has been entered. See, Advisory Action dated March 23, 2004.

Claims 1, 3-5, 7-10, 27-33 and 47-58 are canceled, without prejudice, in the attached Second Amendment Under Rule 116. Entry of the attached Second Amendment Under Rule 116 is requested. The attached Second Amendment Under Rule 116, by only canceling claims, will reduce the issues for appeal without raising new issues requiring further search and/or consideration.

(5) SUMMARY OF THE INVENTION

The present invention provides a process for propagating a mutant herpes simplex virus (HSV) which contains a mutation in its endogenous VP16 gene, wherein the mutation reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein, and which contains a heterologous gene. The process of the claimed invention includes the steps of infecting a cell line with the mutant herpes virus and culturing the cell line, which cell line includes a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide operably linked to a control sequence permitting expression of the polypeptide in the cell line. The nucleic acid sequence of the cell line of the claimed process complements the endogenous gene of the HSV and the nucleic acid sequence of the cell line of the claimed process does not undergo homologous recombination with the endogenous gene. See, independent claim 34 and, for example, page 4, lines 13-31 of the specification.

Support for the details of dependent claim 35 may be found, for example, on page 4, lines 23-26 of the specification.

Support for the details of dependent claim 36 may be found, for example, on page 4, lines 23-25 of the specification.

Support for the details of dependent claim 37 may be found, for example, in originally claim 5.

Support for the details of dependent claim 38 may be found, for example, on page 4, lines 25-26 of the specification.

Support for the details of dependent claim 39 may be found, for example, on page 4, lines 27-31 of the specification.

Support for the details of dependent claim 40 may be found, for example, on page 6, lines 1-7 of the specification and original claim 9.

Support for the details of dependent claim 41 may be found, for example, on page 6, lines 7-9 of the specification.

Support for the details of dependent claim 42 may be found, for example, on page 9, lines 10-21 of the specification and original claim 9.

Support for the details of dependent claim 43 may be found, for example, on page 6, lines 7-9 of the specification.

Support for the details of dependent claim 44 may be found, for example, on page 11, lines 5-6 of the specification.

Support for the details of dependent claim 45 may be found, for example, on page 10, lines 16-19 of the specification.

Support for the details of dependent claim 46 may be found, for example, on page 13, line 23 of the specification.

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(6) ISSUES

The following single (one) issue is presented for appeal:¹

Whether the invention of claims 34-46 would have been obvious to one of ordinary skill in the art in view of Speck *et al* (WO96/04395 A1), Moriuchi *et al* (J. Virol. 1993, vol. 67, pp. 2739-2746) and Purewall (Virology 1994, vol. 198, pp. 385-389).

(7) GROUPING OF THE CLAIMS

The claims stand or fall together.

(8) ARGUMENT

The invention of claims 34-46 would not have been obvious to one of ordinary skill in the art from the combined teachings of Speck *et al* (WO96/04395 A1), Moriuchi *et al* (J. Virol. 1993, vol. 67, pp. 2739-2746) and Purewall (Virology 1994, vol. 198, pp. 385-389). The Section 103 rejection of claims 34-46 over Speck *et al* (WO96/04395 A1), Moriuchi *et al* (J. Virol. 1993, vol. 67, pp. 2739-2746) and Purewall (Virology 1994, vol. 198, pp. 385-389) should be reversed. Consideration of the following in this regard is requested.

¹ The Examiner has not repeated the Section 102 rejection of claims 1, 5 and 7 over Moriuchi *et al* (J. Virol. 1993, vol. 67, pp. 2739-2746) in the Advisory Action dated March 23, 2004. As claims 1, 5 and 7 have been canceled in the attached Second Amendment Under Rule 116, the Section 102 rejection, even if maintained, is moot in view of the attached Second Amendment Under Rule 116.

The presently claimed invention provides methods for propagating herpes simplex virus vectors for gene delivery to the nervous system or elsewhere in the body for, for example, gene therapy, vaccination, or other purposes, or to cells in culture or to animal models of disease (see, page 1, lines 17 to 19 of the specification). Since infection of most cell types with wild-type HSV results in lytic replication or other toxic effects of the virus it is necessary to disable HSV vectors in some way to prevent or minimise these effects (see, page 1, lines 20 to 24 of the specification).

One way to disable HSV vectors to make them safe for administration to humans or animals, or to minimise their cytotoxic effects in cells in culture is to include an inactivating mutation in the gene encoding VP16 (see, page 2 lines 18 to 20 of the specification). VP16 is a virion protein that acts together with cellular factors to trans-activate HSV immediate early (IE) gene promoters after infection (see, page 2 lines 20 to 22). In an HSV virion, VP16 is incorporated into the tegument between the capsid and the virion envelope (see, Weinheimer *et al* (1992) *J. Virol.* 66 page 258, left column lines 9 to 14, already of record and considered by the Examiner on October 24, 2002).

When an HSV infects a cell, VP16 is released from the virion. It then enters the nucleus of the infected cell where it acts to specifically trans-activate the transcription of viral IE genes (see, Weinheimer *et al* page 258, left column lines 14 to 16 and Roizman and Sears (1996) *Fundamental Virology*, Third edition, Chapter 32, page 1055 lines 5 to 10, already of record and considered by the Examiner on October 24, 2002).

In the absence of VP16, transcription of viral IE genes is reduced and so mutation of VP16 is advantageous in the production of an HSV vector (see, page 2, lines 24 to 26 of the specification). However, since VP16 is an essential structural protein, the VP16 gene cannot be deleted from the HSV vector (see, page 2, lines 27 to 28 of the specification). Instead, specific mutations are used which reduce or abolish the trans-activating activity of VP16, but which still allow the VP16 protein to fulfil its structural function (see, page 2, lines 28 to 30 of the specification).

One problem associated with HSV vectors containing a mutation in VP16 which abolishes its trans-activation activity is that such vectors grow only inefficiently on cell lines, thus hindering the growth of vector stocks (see, page 2, line 30 to page 3, line 3).

For other mutations in HSV vectors, such as the deletion of an IE gene, a complementing cell line expressing the mutated gene may be used to grow the vector, provided that the whole gene is deleted from the vector, thus preventing homologous recombination from occurring. If homologous recombination were to occur, revertant HSV containing the wild-type gene would be produced and the resulting HSV vector stocks would not be safe for administration to humans or animals (see, Lachmann and Efstatthiou (1997) Molecular Medicine Today, page 406, right column, last paragraph, of record and considered by the Examiner on October 24, 2002).

The Examiner is understood to believe that Speck *et al* teach that a complementing cell line expressing HSV VP16 may be used to complement the mutation in VP16 in the vectors described therein. However, whilst Speck *et al* may

teach that the HSV vectors may be grown on a complementing cell line, it also teaches that the complementing cell line should not include a VP16 gene.

The vectors disclosed in Speck *et al* have two mutations (a) and (b). Mutation (a) may be

a mutation in the gene corresponding to VP16 (otherwise designated Vmw65 or alpha-TIF) in herpes simplex virus type 1, which is effective to reduce (by comparison with a parent type), or substantially remove, the transinducing properties of the protein encoded by that gene, especially while retaining its structural role. A particular example of such a mutation is the in1814 mutation in HSV1. Further examples of such mutations include...other mutations in the gene corresponding to VP16 that allow growth of the mutant virus in cell culture in the presence of hexamethylene bisacetimide (HMBA)." See, page 3, line 32 to page 4, line 6.

Other examples of mutation (a) are mutations in immediate early genes, e.g. ICP0, ICP4, ICP22 and ICP27 (see, page 4, lines 24 to 36).

Speck *et al* teaches that

"the complementing cell line has been made recombinant by insertion of DNA encoding a product that complements the inactivating mutation (b)" (see, page 6, lines 24 to 25)

and that

"In certain cases it can be convenient to make the complementing cell line complement both of the mutations (a) and (b)." (emphasis added; see, page 6, lines 28 to 30).

Examples of type (a) mutations which may be complemented in the cell line are stated to be IE0, IE4 and IE27 (see, page 6, line 30 to page 7, line 1) and a particular example is a virus that

"is a deletant in respect of gene IE0, and also a deletant in respect of gH." (emphasis added; see, page 7, lines 1 to 6).

Speck *et al.* further state that,

[I]t is preferred, however, not to complement a mutation in the VP16 gene in the complementing cell line, since the effect of the mutation in this particular gene is considered to be obtained where the mutant gene product forms part of the virion. It can be seen that the mutant virus as grown on the complementing cell line is free of admixture with virus that is replication-competent in normal host cells. (Emphasis added.) See page 7 lines 8 to 14.

Thus, Speck *et al.* teach that the mutant virus must not be mixed with replication-competent virus (i.e. wild-type virus produced by homologous recombination). Speck *et al.* also teaches that, since the VP16 gene forms part of the virion, VP16 cannot be deleted and so cannot be complemented in the cell line used for virus growth as this would result in the production of an admixture of viruses with mutant VP16 and viruses with wild-type VP16 that are replication competent. The teaching of Speck *et al.* is, therefore, entirely consistent with the teaching in Lachmann *et al.* (see, above).

For HSV vectors with inactivating mutations in VP16, a complementing cell line which expresses VP16 cannot be used for propagation for two reasons.

The first reason is that given in Speck *et al.* since the VP16 gene cannot be deleted from the virus in its entirety (due to its essential structural role) the inclusion of a wild-type copy of the VP16 gene in a cell line used for virus growth would lead to the generation of a revertant HSV containing wild-type VP16 by homologous recombination (see, also page 3, lines 4 to 11 of the specification).

Secondly, wild-type VP16 protein expressed in the cell line would be incorporated into new HSV virions. Hence, a vector stock produced on such a cell line would include HSV virions containing fully functional VP16 protein. These fully functional VP16 proteins would, on infection of a cell, be released and serve to trans-activate IE gene expression just as the tranactivating mutation was intended to prevent (see, page 3, lines 11 to 14 of the specification).

Thus, HSV vectors grown on a complementing cell line expressing VP16 would not be safe for administration to a human or animal and would produce cytotoxic effects when used to deliver a heterologous gene to a cell in culture.

It has been discovered previously that hexamethylene bisacetimide (HMBA) is capable of directly stimulating IE gene transcription to an extent that when HSV mutants having an inactivating mutation in the VP16 gene are grown on a propagating cell line with HMBA present in the medium, the level of IE gene expression is close to the level reached during infection with wild-type HSV-1 (see MacFarlane *et al* (1992) *J. Gen. Virol.* 73 page 291, left column, last paragraph - of record and indicated as having been considered by the Examiner on October 24, 2002). HMBA was, therefore, used in the prior art to compensate for the inefficient growth in cells in culture of HSV vectors with an inactivating mutation in the VP16 gene (see, page 3, lines 3 to 4 of the specification and Speck *et al*, page 4, lines 4 to 6).

The presently claimed invention provides an alternative, improved method for propagating HSV vector stocks which (a) provides for more efficient HSV growth than

the inclusion of HMBA and (b) is safe to use for the production of HSV vectors for administration to humans or animals. Independent claim 34 provides a process for propagating a mutant herpes simplex virus (HSV) which contains (a) a mutation in its endogenous VP16 gene wherein the mutation reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein; and (b) a heterologous gene. The claimed process includes the steps of infecting a cell line with the mutant herpes virus and culturing the cell line, wherein the cell line contains a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide operably linked to a control sequence permitting expression of the polypeptide in the cell line. The nucleic acid sequence of the cell line complements the endogenous gene and does not undergo homologous recombination with the endogenous gene.

The claims therefore provide methods for propagating an HSV vector, i.e., an HSV containing a heterologous gene, having a transactivation activity-inhibiting mutation in the VP16 gene using a complementing cell line, which expresses a homologue of VP16 from another herpes virus species. The fact that growth of a HSV VP16 mutant on a complementing cell line expressing a VP16 homologue is more efficient than growth on a non-complementing cell line in the presence of HMBA would not have been obvious from any of the cited art, either alone or in combination.

Moreover, there is no suggestion or teaching in the cited prior art that it would have been safe to use a complementing cell line expressing a VP16 homologue in the production of vector stocks.

The advantages of the claimed methods are clear both from the specification and from the post-published literature paper Thomas *et al* (1999) *J. Virol.* 73 pages 7399 to 7409 (of record and considered by the Examiner on October 24, 2002).

The present specification demonstrates that, surprisingly, the use of EHV VP16 in a complementing cell line enhances growth of HSV VP16 mutants more effectively than the inclusion of HMBA in the growth media. This is clear from, for example, Example 2 at page 18, line 24 to page 19, line 26 of the specification.

Example 2 compares the yield of wild-type virus (17+) and two viruses containing an inactivating mutation in VP16 (in1814 and 1764). As can be seen from the Table at page 19, lines 11 to 20, inclusion of HMBA in the medium enhances growth of in1814 and 1764 approximately ten fold. Growth of both these viruses is enhanced by a greater degree when the cell line used to grow the viruses expresses EHV gene 12 (EHV-VP16). The yield of in1814 was enhanced approximately 60 fold and the yield of 1764 was enhanced approximately 40 fold when EHV-gene 12 was expressed in the cell line used for virus growth. A further increase in yield was observed when HMBA was included in the medium and EHV-gene 12 was present in the cell line. Thus, as stated at page 19, lines 21 to 26; the specification teaches that,

EHV-VP16 can complement the deficiency in virus growth caused by the inclusion of inactivating mutations in the gene for VP16, such as in virus in1814 (Ae et al., 1819). Such viruses can be grown to near wild-type levels, the level of complementation being greater than that achieved by the inclusion of HMBA in the media which has previously been reported to increase the efficiency of growth of HSV with mutations in VP16 (MacFarlane et al, 1992)

The improved efficiency in HSV growth observed when EHV gene 12 is present in the complementing cell line compared to HMBA was not obvious from the prior art.

Purewal *et al* teaches that EHV gene 12 is capable of transactivating HSV IE gene promoters but provides no information as to the effectiveness of using a complementing cell line expressing EHV gene 12 to grow HSV VP16 mutants. In fact, Purewal *et al* does not even teach or suggest that EHV gene 12 may be included in a complementing cell line.

Moriuchi *et al* demonstrates that VZV ORF 10 can activate HSV IE gene promoters and that a cell line expressing VZV ORF 10 to complement the HSV-1 in1814 mutant. Moriuchi et al provides no indication as to the efficiency of growth of HSV-1 in1814 on such a complementing cell line compared to growth in the presence of HMBA. Since Moriuchi *et al* is concerned only with elucidating whether VZV ORF10 has a trans-activation activity equivalent to that of HSV VP16, and not with methods of propagating HSV vectors, there is no reason why Moriuchi *et al* would have wished to carry out such a comparison.

There is, therefore, nothing in Purewal *et al* or Moriuchi *et al* to suggest that use of a complementing cell line expressing a VP16 homologue is any better than HMBA in promoting IE gene expression. Furthermore, the result is surprising since MacFarlane *et al* (of record and considered by the Examiner on October 24, 2002) teaches that the levels of IE gene transcription achieved for mutant HSV in the presence of HMBA are close to those achieved for wild-type HSV in the absence of HMBA (page 291, left column, last paragraph).

One of ordinary skill in the art would not have expected a VP16 homologue from another species to transactivate HSV IE gene promoters as effectively as HSV VP16 itself.

For example, Moriuchi *et al* shows that growth of in1814 on cells expressing VZV ORF10 (V10R-18) is enhanced three to eight fold compared to control cells, whilst growth on cells expressing HSV VP16 (16-8) is enhanced 14 fold (see, page 2743, left column, lines 16 to 20 and Table 2). Therefore, the ordinarily skilled person would not have expected the growth of HSV VP16 mutants on complementing cell lines to be better than in the presence of HMBA.

The fact that use of such a cell line provides an improved method for propagating HSV VP16 mutants is, therefore, an unexpected result.

Moreover, the use of a complementing cell line expressing a VP16 homologue is better than addition of HMBA to the growth medium because HMBA does not effectively complement the growth of vectors which contain disabling mutations in the ICP27 gene

in addition to a mutation in the VP16 gene which inactivates trans-activation activity (see, Thomas et al page 7402, left column, lines 5 to 13). However, a complementing cell line which expresses EHV gene 12 (a homologue of VP16) can be used to efficiently grow such a double mutant (see, Thomas et al page 7402, left column, lines 35 to right column line 2).

Moriuchi *et al* is not concerned with methods of propagating an HSV VP16/ICP27 double mutant. Neither are any of the other cited documents. Thus, the improved growth of an HSV VP16/ICP27 double mutant seen using a complementing cell line expressing EHV gene 12 would not have been obvious from the cited art.

Beyond providing a more efficient method of propagating HSV vectors than the methods used in the cited art, the presently claimed methods are also safe for propagating vector stocks intended for administration to humans or animals.

The appellants have discovered, for the first time, that homologues of VP16 from other species have nucleic acid sequences sufficiently divergent from the HSV VP16 nucleic acid sequence such that the VP16 gene in an HSV vector being propagated will not undergo homologous recombination with a VP16 homologue expressed in a cell line used to grow the HSV vector. Thus, unlike when a cell line expressing HSV VP16 is used to propagate an HSV, no revertant HSV vectors containing a wild-type VP16 gene with normal trans-activation activity will be produced. The presently claimed method thus allows vector stocks to be propagated safe in the knowledge that the vector stocks produced will not contain any HSV vectors containing a wild-type VP16 gene (see, page

3, line 29 to page 4, line 4 of the specification and Thomas *et al*, page 7400, left column lines 35 to 41 and page 7408, left column lines 5 to 9).

These advantages are not suggested or even addressed in Moriuchi *et al* nor in Purewal *et al*, which are both concerned only with investigating the trans-activation activites of VZV ORF10 and EHV gene 12, respectively. Accordingly, neither of these documents provides any teaching or suggestion as to the possibility of homologous recombination between a VP16 homologue expressed in a cell line and a mutant HSV VP16 gene in an HSV vector.

The appellants have also discovered that the protein encoded by the gene complementing the HSV VP16 gene must not be incorporated into the HSV virions produced in the complementing cell line (see, page 3 lines 11 to 14 of the specification) is a further important safety factor. The fact that homologues of HSV VP16 from other species are not incorporated into HSV virions is demonstrated for EHV gene 12 in Thomas *et al*. Thomas *et al* shows that HSV VP16 mutants grown on EHV gene 12 complementing cell lines exhibit identical growth curves to HSV VP16 mutants grown on non-engineered cells and that no signal for EHV gene 12 is seen in Western blots of viral samples grown on either of the two cell types (see, page 7402, right column, last paragraph and Figure 6). Since EHV gene 12 is not incorporated into HSV virions when HSV vectors are propagated on an EHV gene 12 expressing cell line, the deficiency in IE gene expression resulting from the lack of VP16 transactivating activity will be

retained. This is an important aspect of the presently claimed invention which could not have been predicted from the cited art.

It had been previously shown by Weinheimer *et al* that VP16 protein expressed by a complementing cell line is incorporated into HSV virions (see, Weinheimer et al page 263, left column, last three lines to right column line 18), both when the HSV being grown is a VP16 deletion mutant and when the HSV is wild-type (see, page 263, right column, lines 10 to 13).

Moriuchi *et al*, which describes the growth of in1814 mutant HSV on cell lines expressing VZV ORF10, provides no teaching as to whether or not VZV ORF10 is incorporated into HSV virions. Moriuchi *et al* does, however, make the general statement that

"[I]ke VP16, VZV ORF10 protein is incorporated into the tegument of virions" (page 2739 lines 5 to 7).

Therefore, a person ordinarily skilled in the art, knowing that VZV ORF10 complements the transactivation role of VP16 and that, like VP16, VZV ORF10 is a tegument protein, would have expected VZV ORF10 to complement the structural role of VP16.

Thus, in view of the teachings of Weinheimer *et al* and Moriuchi *et al*, one of ordinary skill in the art would have expected VZV ORF10 and other homologues of VP16 to be incorporated into HSV virions and the contrary results described in Thomas *et al* would not have been obvious or expected from the cited art.

In conclusion, there was nothing in the cited art to teach or suggest that use of complementing cell line expressing a homologue of VP16 from different species may provide an improved means for propagating mutant HSV vector stocks. There was also nothing in any of the cited prior art documents to teach or suggest that the problems associated with using HSV VP16 expressing complementing cell lines may be overcome by using a homologue of VP16 from another species instead of HSV VP16. In particular, none of the cited prior art documents indicate that homologous recombination does not occur between the HSV VP16 gene and the homologue of VP16 from another species. The cited prior art does also not provide any teaching as to whether or not proteins encoded by HSV VP16 homologues in other species incorporated into HSV virions. Accordingly, the presently claimed invention would not have been obvious to a person of ordinary skill in the art from the cited combination of art.

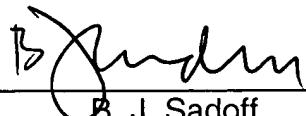
Reversal of the Section 103 rejection of claims 34-46 is requested.

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Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____



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34. A process for propagating a mutant herpes simplex virus (HSV) comprising:

(a) a mutation in its endogenous VP16 gene wherein the mutation reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein; and

(b) a heterologous gene;

which process comprises infecting a cell line with the mutant herpes virus and culturing the cell line,

wherein the cell line comprises a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide operably linked to a control sequence permitting expression of the polypeptide in said cell line and wherein the nucleic acid sequence (i) complements the endogenous gene and (ii) does not undergo homologous recombination with the endogenous gene.

35. A process according to claim 34 wherein the functional equivalent of the HSV VP16 polypeptide is encoded by a herpes virus gene selected from a bovine herpes virus gene and an equine herpes virus gene.

36. A process according to claim 35 in which the herpes virus gene is equine

virus gene is equine herpes virus 1 gene 12, or the bovine herpes virus gene BTIF.

37. A process according to claim 34 wherein the control sequence comprises a constitutively active promoter or an inducible promoter.

38. A process according to claim 34 wherein the HSV is an HSV-1 or HSV-2.

39. A process according to claim 34 wherein the mutant herpes simplex virus comprises additional mutations which functionally inactivate one or more additional endogenous genes of said virus and the cell line comprises additional nucleic acid sequences encoding functional herpes virus genes which complement said additional functionally inactive endogenous genes.

40. A process according to claim 39 wherein said additional nucleic acid sequences encode at least one of HSV-1 ICP27, HSV-1 ICP4, an equivalent of said HSV-1 ICP27 in HSV-2 or another herpes virus, and an equivalent of said HSV-1 ICP4 in HSV-2 or another herpes virus.

41. A process according to claim 40 in which at least one of said HSV-1 ICP27 or said equivalent is driven by the ICP27 promoter and said HSV-1 ICP4 or equivalent is driven by the MMTV LTR promoter.

42. A process according to claim 40 wherein said additional nucleic acid sequences additionally encode HSV-1 ICP27 or an equivalent thereof in HSV-2 or another herpes virus.

43. A process according to claim 42 wherein the HSV-1 ICP27 or equivalent thereof is driven by the ICP27 promoter.

44. A process according to claim 34 which the heterologous gene is operably linked to a control sequence permitting expression of the heterologous gene in a mammalian cell.

45. A process according to claim 34 wherein the heterologous gene is an HSV gene that is not operably linked to the viral control sequence with which it is naturally associated.

46. A process according to claim 34 wherein the heterologous gene encodes a polypeptide of therapeutic use.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER RULE 116
EXPEDITED HANDLING PROCEDURES

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C# M#

C/A.U. 1648

Examiner: Li

Date: June 29, 2004

Mail Stop AF

Commissioner for Patents

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Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

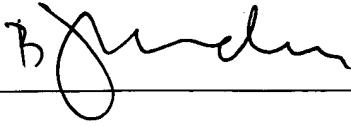
 Correspondence Address Indication Form Attached.**Fees are attached as calculated below:**

Total effective claims after amendment	0	minus highest number		
previously paid for	20	(at least 20) =	0	\$ 18.00
Independent claims after amendment	0	minus highest number		
previously paid for	3	(at least 3) =	0	\$ 86.00
If proper multiple dependent claims now added for first time, add \$290.00 (ignore improper)			\$	0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) (\$110.00/1 month; \$420.00/2 months; \$950.00/3 months)			\$	950.00
Terminal disclaimer enclosed, add \$ 110.00			\$	0.00
<input type="checkbox"/> First/second submission after Final Rejection pursuant to 37 CFR 1.129(a) (\$770.00)			\$	0.00
<input type="checkbox"/> Please enter the previously unentered , filed				
<input type="checkbox"/> Submission attached				
			Subtotal	\$ 950.00
If "small entity," then enter half (1/2) of subtotal and subtract			-\$	475.00
<input checked="" type="checkbox"/> Applicant claims "small entity" status. <input type="checkbox"/> Statement filed herewith				
Rule 56 Information Disclosure Statement Filing Fee (\$180.00)			\$	0.00
Assignment Recording Fee (\$40.00)			\$	0.00
Other: Less \$475 paid separately herewith and listed on attached cover to Appeal Brief				-475.00
			TOTAL FEE ENCLOSED	\$ 0.00

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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BJS:

NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: 

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

COFFIN et al.

Serial No. 09/762,098



Atty Dkt. 117-340

C# M#

TC/A.U.: 1648

Examiner: Li

Date: June 29, 2004

Title: CELL LINES FOR THE PROPAGATION OF MUTATED HERPES VIRUSES

Mail Stop Appeal Brief - Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Sir:

Correspondence Address Indication Form Attached.

NOTICE OF APPEAL

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner. (\$ 330.00) \$

An appeal **BRIEF** is attached in triplicate in the pending appeal of the above-identified application (\$ 330.00) \$ 330.00

Credit for fees paid in prior appeal without decision on merits -\$ ()

A reply brief is attached in triplicate under Rule 193(b) (no fee)

Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) (\$110.00/1 month; \$420.00/2 months; \$950.00/3 months; \$1480.00/4 months) \$ 950.00

SUBTOTAL \$ 1280.00

Applicant claims "Small entity" status, enter ½ of subtotal and subtract -\$ (640.00)
 "Small entity" statement attached.

SUBTOTAL \$ 640.00

Less month extension previously paid on -\$ (0.00)

TOTAL FEE ENCLOSED \$ 640.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140**. A duplicate copy of this sheet is attached.

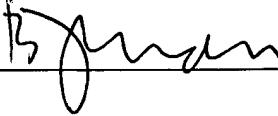
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